REMARKS

1. Restriction and Election of Species Requirements

The Examiner has maintained the restriction requirement, specifically noting that the election of (a) EpCAM and (b) Lewis Y is "a restriction requirement and not a species election". The Examiner has made the restriction requirement final in the outstanding Office Action.

Applicants continue to assert that the restriction requirement is improper, and that the attempt to limit Applicants to the elected species is also contrary to the appropriate procedure for examination of generic and Markush-type claims.

With respect to the restriction between the two groups of claims, the Examiner's position is premised on an argument that the references cited in the International Search Report indicate that the special technique or feature that links the inventions or groups of inventions together is not novel. Applicants assert that the linking feature is indeed novel, as discussed further below with respect to the prior art rejections. Thus, once the Examiner agrees that the claims are novel and non-obvious, then the restriction requirement should be withdrawn.

With respect to the attempt to limit Applicant's claims to only the elected species, Applicants previously urged that this action by the Examiner is improper and contrary to binding legal precedent. Those arguments are fully set forth in Applicants' response of February 5, 2007, and will not be repeated herein. But Applicants again note that the Examiner's apparent refusal to substantively examine Applicants' generic claims is contrary to "elementary patent law" which, as explained by Judge Rich, fully entitles Applicants to generically claim their invention and, while the USPTO may limit an application to a single invention, that "discretionary power to limit one application to one invention is no excuse at all for refusing to examine a broad generic claim – no matter how broad, which means that no matter how many independently patentable inventions fall within it." (emphasis added) *In re Weber*, 198 USPQ 328, 331-332 (J. Rich, concurring, CCPA 1978).

2. Claim Rejections

The Examiner objects to claims 1-5, 7, 8 and 23 as containing "non-elected inventions". Applicants will appropriately amend the generic claim following an indication of allowability of the elected species.

3. Claim Rejections – 35 USC § 112, 2nd Paragraph

Claim 1 has been amended in a manner believed to obviate the Examiner's objection.

4. Claim Rejections – 35 USC § 112, 1st Paragraph

Although Applicants do not concede the propriety of the Examiner's objection with respect to the use of the phrase "vaccine", claim 3 has been amended in a manner believed to obviate the Examiner's rejection.

5. Claim Rejections – 35 USC § 102

Claims 1-3, 5, 7 and 8 have been rejected under 35 USC § 102(b) as being anticipated by WO 01/35989 A2. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

WO 01/35989 discloses the purification of anti-idiotypic antibodies using resin bound specific antibodies directed against EpCAM and Lewis Y for the production of autologous vaccines. According to this document,t the combined use of such antibodies is restricted only to the purification of other antibodies. The anti-idiotypic antibodies produced by the methods described in this document do not comprise an epitope of a cellular surface protein or an epitope from aberrant protein glycosylation as defined in the present claim 1. Anti-idiotypic antibodies according to WO 01/35989 are isolated by immunoaffinity chromatography using antibodies obtained by such a purification method may show similarities to the epitopes of claim 1, they do not comprise these epitopes themselves but can, at most, only mimic epitopes. Claim 1 recites that the antigens include the epitope of a cellular surface protein and an aberrant protein glycosylation. Thus, such mimics and anti-idioytpic antibodies are excluded from claim 1.

The Examiner will note that the present application distinguishes between the epitopes and the mimics of the epitope (p. 10, middle 2nd paragraph) and since the present claim 1 comprises the limitation that the antigen must have an epitope (but not the mimic of the epitope) of the respective antigens, Applicants submit that renders the claims novel over the anti-idiotypic antibodies of WO 01/35989.

Anti-idiotypic antibodies comprise only mimics of an antigen epitope in their variable region. The amino acids of the variable region are arranged in such a way to have a similar appearance of a given epitope which has a completely different chemical structure. In particular, in the case of Lewis-Y structure (a carbohydrate) the anti-idiotypic antibody and its variable region fall into a completely different category (proteins). Furthermore, with polyclonal antibodies according to the WO 01/35989 a composition of multitude of different mimics is obtained. Contrary thereto, the antigen epitopes of the present claims are generally isolated, chemically well defined compounds. In addition, epitope mimics of the anti-idiotypic antibodies (that can be isolated by the procedure of the WO 01/35989) only comprise such epitopes which are recognized by the antibodies which are immobilized on the Sepharose resin. Accordingly, reconsideration and withdrawal of the rejections are requested.

6. Claim Rejections – 35 USC § 103

6.1 Based on WO 01/35989 A2 as the Primary Reference

Claims 1-5, 7 8 and 23 have been rejected as obvious over WO 01/35989 in combination with Maruyama et al., Sabbatini et al. and Berthelsen et al. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

Maruyama et al. describes experimental differences in the use of a colorectal carcinoma (CRC)-associated antigen, termed GA 733 (also known as CO17-1A and EpCAM), and a monoclonal anti-idiotypic antibody directed to the anti-CRC monoclonal antibody and thus mimicking one epitope of the antigen. Clinically it was found that the antigen was superior to the anti-idiotypic antibody for inducing specific humoral and cellular responses, and it is asserted

that anti-idiotypic antibody vaccines may be found to be less likely to induce an immunity to antigens (s. p. 124, first paragraph and p. 129, last paragraph).

The Examiner alleges that a combination of the Maruyama et al. article with WO 01/35989 would have made it obvious to select EpCAM and Lewis Y antigens, since the skilled man in the art would recognize the superiority of the antigens themselves over the anti-idiotypic antibodies of the EpCAM and Lewis Y antigens. On the Contrary, Maruyama et al., would actually support the above mentioned argumentation in support of novelty in that the antigens are significantly different over structures which only mimic such an antigen epitope. However, Maruyama et al. only describes the effects of the antigen itself and the anti-idiotypic antibody as a whole, but not the differences between epitopes and mimics of epitopes.

With regard to non-obviousness in view of the combination of WO 01/35989 and Maruyama et al., although WO 01/35989 discloses the purified preparation of an EpCAM and Lewis Y anti-idiotypic antibody, it actually does not suggest the use of a combination, over the improved results achieved by use of such a combination. This improved effect is shown in the examples of the present application, in particular on p. 31, 2nd and 3rd paragraphs (for a combination of antibodies), and on p. 32 (showing immunization with the antigens). Such an improved effect is not apparent from either WO 01/35989, Maruyama et al. or a combination of the two references.

Furthermore, the combined preparation of EpCAM and Lewis Y antibodies according to WO 01/35989 cannot simply be adapted to a combined pharmaceutical preparation of antigens. When using antigens, the lower specificity and higher (unspecific) immunogenicity has to be considered (s. e.g. Maruyama et al., p. 124, 1st complete sentence). Therefore, a host challenged with an antigen will suffer from an increased and more severe immune reaction in combination to a challenge with an anti-idiotypic antibody. This effect is further potentiated by the combined use of two antigens and thus the presented inventive combination does not appear recommended in view of the state of the art. Additionally, the increased protective immune reaction of the antigen in comparison to the anti-idiotypic antibody mentioned by the Examiner is not at all assured. The Examiner has not considered that Maruyama et al. describes a study where it was

reported that the anti-idiotypic antibodies mimicking a bacterial antigen primed protection whereas the antigen itself did not (s. Maruyama et al., p. 130, 2nd paragraph). Therefore, there are several reasons which would discourage the skilled man in the art, or at least provide no incentive, for trying to prepare a combined vaccine with EpCAM and Lewis Y antigens in particular – or generally according to claim 1 of the present application.

Furthermore, prior to the present invention, it was known that the use of an antigen in a therapy can be problematic over the use of anti-idiotypic antibodies (see enclosed documents Luo et al., J Biol Chem 275(21): 16146 (2000) and Kieber-Emmons et al., J Immunol 165: 623-627 (2000)). These references argue that carbohydrate Lewis Y (LeY) is generally problematic for induction of a T-cell dependent immune response, and consequently the use of peptide/protein mimics (including anti-idiotypic antibodies) would be the primarily preferred way to go based on the state of the art.

Luo et al. teaches that antibodies originally directed against LeY in mice can cross-react with other carbohydrate structures and "paradoxically, this generated humoral response can fail to recognize natively present LeY" (p. 16146, right col., 2nd half of 2nd para.). On the other hand, peptide mimics "can bind to isolated antibodies by the same mechanisms as the original carbohydrate antigen" (p. 16153, left col., last para.). The problem of anti-LeY antibody cross-reactivity (if the antibody is directed at the natural LeY antigen) is also discussed by Kieber-Emmons et al. (abstract). According to this article "peptides that mimic carbohydrate structures have significant advantages as vaccines" (p. 623, left col., 2nd para.) based on different antigen processing of the Th1 immune response as compared to carbohydrate-protein conjugate processing.

Therefore, the present invention is non-obvious over the state of the art by providing a surprisingly efficient way of using such carbohydrate antigens in combination with an antigen with an epitope of a cellular surface protein or an antibody against a cellular surface protein which specifically directs the immune response in a surprisingly synergistic way.

The co-cited document Sabbatini et al. describes the treatment of cancer patients with a Lewis Y antigen together with an immunological adjuvant. Similar to Maruyama et al., this treatment with a single antigen preparation (which might or might not be superior to an anti-idiotypic antibody) cannot suggest or hint at the present invention or the comprised effect of a combined therapy.

U.S. Patent No. 6,455,290 B1 to Berthelsen et al. discloses sequences of a tankyrase homologue protein and is completely unrelated to the present invention. The Examiner cites this document in order to show that making intravenous tolerable preparations comprising antibodies are known in the art. However, the cited passages (col. 20, l. 45-61) relate to screening methods for low molecular weight organic molecules (contrary to polypeptides) which can be used in such pharmaceutical compositions. Of course, the inventive tumor antigens or antibodies are not low molecular weight organic molecules.

For these reasons, Applicants submit that the rejection should be withdrawn.

6.2 Based on U.S. Patent 5,738,867 to Spitler as the Primary Reference

Spitler describes an anti-tumor preparation with an antigen or anti-idiotypic antibody in a liposome preparation. As antigen GS-733-2 or CO 17-1A (which is EpCAM according to Maruyama et al.) is mentioned. Claim 2 of Spitler mentions that in the anti-tumor vaccine an "additional synthetically prepared tumor associated antigen" can be present. However, the mere statement that a preparation may also have two antigens does not provide any insights in the improved effects of the specifically selected antigens as defined in claim 1. In his assertions, the Examiner, assumes that "it is known in the art that using two cancer drugs often results in synergistic effects", and that therefore it would be obvious for a skilled man in the art to combine this document e.g. with the document of Sabbatini et al. which describes the use of a Lewis Y antigen in a tumor vaccine and arrive at the present invention. However, this assertion of an expected synergistical effect is completely unfounded and pure hindsight.

When using two antigens in one preparation it is expected that – if those antigens do not negatively interfere with each other's functionality – at best each antigen would result in its own

single effect and the sum of those effects could be observed. However, a synergistic effect requires that the observed effect would be increased as compared to the sum of each single effect of the antigens. Such an increased effect is shown by the examples in the present application and is completely surprising and inventive over the state of the art.

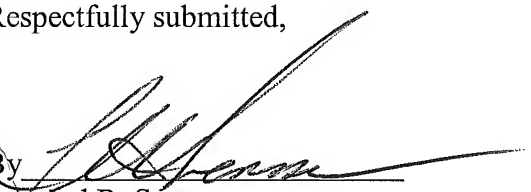
For the above reasons, reconsideration and withdrawal of the rejections and early allowance of all the claims are requested.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a two (2) month extension of time for filing a reply in connection with the present application, and the required fee of $450.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to our Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

Dated: September 10, 2007

Respectfully submitted,

By 

Leonard R. Svensson
Registration No.: 30,330
BIRCH, STEWART, KOLASCH & BIRCH, LLP
12770 High Bluff Drive
Suite 260
San Diego, California 92130
(858) 792-8855
Attorney for Applicant